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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/761,530	KOEBERL ET AL.	
	Examiner	Art Unit	
	GANAPATHIRAMA RAGHU	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-12,14-16,18,21,22,24-73,75-77 and 79-82* is/are pending in the application.

4a) Of the above claim(s) *30-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-12,14-16,21,22,24-29,73,75-77 and 79-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/11/08; 08/07/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/07/08 has been entered.

Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-73, 75-77 and 79-82 are pending in this application, claims 30-72 are withdrawn as they are drawn to non-elected inventions and thus claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 are under consideration in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 08/11/08 and 08/07/08 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner is considering the IDS statement.

Withdrawn-Claim Rejections 35 USC § 102

Claims 1-2, 5, 8-12, 14-16, 18 and 21-29 rejected under 35 U.S.C. 102(b) as being anticipated by Amalfitano et al., (WO 02/098466 A1, 2002, in IDS) when given the broadest interpretation is being withdrawn due to claims amendments and persuasive arguments by the applicants.

Maintained-Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 8-11, 18, 21, 22 and 24-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Bree et al., (WO 00/34451, 2000, in IDS) when given the broadest interpretation. Claims 1, 2, 8-11, 18, 21, 22 and 24-29 are directed to any isolated nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to a human acid α-gluocosidase (GAA) polypeptide and comprising any secretory signal sequence including variants, mutants and recombinants, wherein said secretory signal sequence replaces the leader sequence of native human GAA and further comprising a polynucleotide from any 3' untranslated region, vector comprising said polynucleotides, host cell comprising said vector, a method of delivering said vector comprising said polynucleotide to a host cell and a method of expressing encoded polypeptide.

Van Bree et al., (*supra*) disclose compositions comprising polynucleotides encoding the human GAA with native secretory signal sequence and also suggest said GAA can be operably linked to other signal peptides (page 9, lines 16-30), vectors, methods of expression of encoded polypeptides, a method of expressing said polypeptide in many mammalian cultured cells such as CHO, 293 and methods to generate transgenic animals (*in vivo*) comprising polynucleotides encoding human GAA (Summary of the Invention: pages 3-28; especially pages 7, 9 and 10). In addition said

reference teaches that: i) lysosomal proteins such as human GAA undergo proteolytic processing, in which the first event is removal of the signal polypeptide and renders the protein soluble (page 7, lines 26-32) and ii) the native secretion signal sequence (leader sequence) linked to the lysosomal protein coding sequence is replaced with a signal sequence that targets the processing enzyme to the endoplasmic reticulum (page 11, lines 29-35), providing evidence that the native leader sequence of human GAA can be replaced with any signal sequence of interest such as secretory signal sequence. Therefore, the reference of Van Bree et al., anticipates claims 1, 2, 8-11, 18, 21, 22 and 24-29 of the present invention.

In response to the above rejection, applicants have traversed on the basis that:

"However, no where Van Bree et al., seen [sic 'm'] to teach the replacement of the leader sequence of native human GAA with a secretory signal sequence as required by the instant claims. The examiner is urged to point out where such teaching is found or withdraw the rejection".

Reply: Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons:

The evidence that replacing the leader sequence of native human GAA with a secretory signal sequence and demonstration of biological activities in said chimeric proteins were well known in the art and also envisaged by Van Bree et al., especially the native secretion signal sequence (leader sequence) linked to the lysosomal protein coding sequence is replaced with a signal sequence that targets the processing enzyme to the endoplasmic reticulum (page 11, lines 29-35) or any signal sequence of interest

such as mammary gland specific signal sequences like α-lactalbumin, α-casein, β-casein that can be potentially employed as signal sequences for the expression of human GAA transgene, recovery of the expressed polypeptide and use of purified polypeptide for the treatment of patients having genetic or other deficiency resulting in insufficiency of functional lysosomal GAA enzyme (in pages 3-28; especially pages 7, 9 and 10 page 15; Example 3-4, pages 25-28). Thus, providing evidence that recombinant human GAA comprising heterologous secretion signals wherein native leader sequence has been replaced is correctly processed and biologically active, thus implying unaltered glycosylation and correct processing for the maintenance of biological activity.

New-Claim Rejections 35 USC § 103

Claim amendments have necessitated a new rejection.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5, 12, 14-16, 73, 75 and 80-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Bree et al., (WO 00/34451, 2000, in IDS) as applied to claims 1, 2, 8-11, 18, 21, 22 and 24-29 above, and further in view of Amalfitano et al., (WO 02/098466 A1, 2002, in IDS).

Van Bree et al., (*supra*) disclose compositions comprising polynucleotides encoding the human GAA with native secretory signal sequence and also suggest said GAA can be operably linked to other signal peptides (page 9, lines 16-30), vectors, methods of expression of encoded polypeptides, a method of expressing said polypeptide in many mammalian cultured cells such as CHO, 293 and methods to generate transgenic animals comprising polynucleotides encoding human GAA (Summary of the Invention: pages 3-28; especially pages 7, 9 and 10). In addition said reference teaches that: i) lysosomal proteins such as human GAA undergo proteolytic processing, in which the first event is removal of the signal polypeptide and renders the protein soluble (page 7, lines 26-32) and ii) the native secretion signal sequence (leader sequence) linked to the lysosomal protein coding sequence is replaced with a signal sequence that targets the processing enzyme to the endoplasmic reticulum (page 11, lines 29-35), providing evidence that the native leader sequence of human GAA can be replaced with any signal sequence of interest such as secretory signal sequence.

However, Van Bree et al., (*supra*) are silent regarding said polynucleotide encoding the human GAA is operably linked to transcriptional control element operable in liver cells (as in claim 5), wherein the vector is an adeno-associated virus (AAV) vector (as in claims 12), a pharmaceutical composition comprising said polynucleotide and vector (as in claims14-16, and 80-82), said polynucleotide encodes the amino acid residues 28-952 of SEQ ID NO: 2 (as in claims 73 in part and 75).

Amalfitano et al., (*supra*) teach adenovirus and adeno-associated virus vectors comprising polynucleotides encoding chimeric polypeptides comprising a secretory

signal sequence operably linked to human GAA including the amino acid residues 28-952 of SEQ ID NO: 2 (lines 13-26, page 22) and a method of producing said polypeptide in many mammalian cultured cells such as CHO, 293 and *in vivo* in heaptocytes (Summary of the Invention: pages 3-41; especially pages 6, 7, 12, 22, 26, 28-30, 35, 41 and Examples 1, 4, 9, and 13), and pharmaceutical compositions comprising said polynucleotides and vector (entire document).

Therefore, it would have been obvious to a person of ordinary skill in the art to combine the teachings of Van Bree et al., and Amalfitano et al., to produce a polynucleotide configured in a suitable vector and encoding a therapeutic polypeptide composition comprising human acid alpha-glucosidase (GAA), said therapeutic polypeptide comprising any secretory signal sequence of interest that is suitable for targeting said polypeptide to any cell or tissue of interest depending on the clinical condition that need to be rectified. Motivation to generate a therapeutic GAA comprising a secretory signal peptide derives from the fact that therapeutic lysosomal enzyme polypeptides are endowed with properties that enable them to be efficiently targeted to sub-cellular compartments such as lysosomes or endoplasmic reticulum and golgi apparatus for post-translational modification of said therapeutic proteins and for efficient processing and transport in the target tissues. The expectation of success is high, because Van Bree et al., disclose compositions comprising polynucleotides encoding the human acid alpha-glucosidase (GAA) with native secretory signal sequence and also suggest said GAA can be operably linked to other signal peptides (page 9, lines 16-30), vectors, methods of expression of encoded polypeptides, a method of

expressing said polypeptide in many mammalian cultured cells such as CHO, 293 and methods to generate transgenic animals comprising polynucleotides encoding human GAA (Summary of the Invention: pages 3-28; especially pages 7, 9 and 10). In addition said reference teaches that: i) lysosomal proteins such as human GAA undergo proteolytic processing, in which the first event is removal of the signal polypeptide and renders the protein soluble (page 7, lines 26-32) and ii) the native secretion signal sequence (leader sequence) linked to the lysosomal protein coding sequence is replaced with a signal sequence that targets the processing enzyme to appropriate sub-cellular compartments or tissue of interest. Similarly, Amalfitano et al., teach adenovirus and adeno-associated virus vectors comprising polynucleotides encoding chimeric polypeptides comprising a secretory signal sequence operably linked to human GAA including the amino acid residues 28-952 of SEQ ID NO: 2 (lines 13-26, page 22) and a method of producing said polypeptide in many mammalian cultured cells such as CHO, 293 and in vivo in heaptocytes (Summary of the Invention: pages 3-41; especially pages 6, 7, 12, 22, 26, 28-30, 35, 41 and Examples 1, 4, 9, and 13) and pharmaceutical compositions comprising said polynucleotides (entire document). Therefore, Claims 5, 12, 14-16, 73, 75 and 80-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Bree et al., (WO 00/34451, 2000, in IDS) as applied to claims 1, 2, 8-11, 18, 21, 22 and 24-29 above, and further in view of Amalfitano et al., (WO 02/098466 A1, 2002, in IDS).

Claims 3, 4, 73, 75, 77, 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Bree et al., (WO 00/34451, 2000, in IDS), Amalfitano et al., (WO

02/098466 A1, 2002, in IDS) and further in view of Heus JH (US Patent No.: 6,858,425 B1, claiming priority date of Application No.: 09/454,466 filed on 12/03/99) and Haseltine et al., (WO 2005/003296 A2, claiming priority date of Application No.: 60/441,305 filed on 01/22/03). Rejection of claims 1-2, 5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75 and 80-82 under 35 U.S.C. 103(a) as being unpatentable over Van Bree et al., and Amalfitano et al., is discussed above. Van Bree et al., and Amalfitano et al., teach isolated nucleic acids expressing lysosomal polypeptides as chimeric polypeptide comprising secretory signal sequence operably linked to human acid alpha-glucosidase (GAA), the full-length polypeptide, cleaved and mature forms of polypeptides including chimeric polypeptides comprising heterologous secretory signal sequences operably linked to said polypeptides. Van Bree et al., and Amalfitano et al., are silent regarding said polynucleotide comprising the 3' untranslated region of SEQ ID NO: 3 (as in claim 79) or said polynucleotide encoding a fusion polypeptide comprising SEQ ID NO: 5, an albumin signal peptide sequence (as in claims 5 and 73 in part).

Heus JH et al., have disclosed the human alpha glucosidase (GAA) gene, vector constructs and the 3' untranslated region sequence of said gene (entire document).

Haseltine et al., disclose the albumin signal peptide sequence of SEQ ID NO: 5 (as in claims 5 and 73 in part) and methods for fusing said signal peptide sequence linked to various therapeutic proteins as fusion proteins for use in gene therapy techniques.

Therefore, it would have been obvious to a person of ordinary skill in the art to combine the teachings of Van Bree et al., Amalfitano et al., Heus JH., and Haseltine et

al., to produce an isolated nucleic acid encoding a chimeric therapeutic polypeptide such as human GAA comprising the 3' untranslated region of the human GAA polynucleotide sequence and further said encoded chimeric polypeptide comprising the albumin secretory signal peptide. Motivation to generate a therapeutic GAA comprising a secretory signal peptide derives from the fact that therapeutic lysosomal enzyme polypeptides are endowed with properties that enable them to be efficiently targeted to sub-cellular compartments such as lysosomes or endoplasmic reticulum and golgi apparatus for post-translational modification of said therapeutic proteins and for efficient processing and transport in the target tissues. The expectation of success is high, because Van Bree et al., and Amalfitano et al., teach the use of lysosomal polypeptides such as human acid alpha-glucosidase (GAA) wherein leader sequence of native human GAA has been replaced with a heterologous secretory signal sequence, distinct advantages and the method of use of said polypeptide for therapeutic purposes and Heus JH., and Haseltine et al., teach the use of 3' untranslated region of the human GAA polynucleotide sequence and albumin secretory signal peptide as a chimeric polypeptide for effective targeting of said therapeutic polypeptides to clinically significant target tissues. Therefore, claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75, 77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Bree et al., (WO 00/34451, 2000, in IDS) Amalfitano et al., (WO 02/098466 A1, 2002, in IDS) and further in view of Heus JH (US Patent No.: 6,858,425 B1, claiming priority date of Application No.: 09/454,466 filed on 12/03/99) and Haseltine et al., (WO 2005/003296 A2, claiming priority date of Application No.: 60/441,305 filed on 01/22/03).

Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75, 77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., and further in view of Martin et al., (WO 00/47741, 2000). Rejection of claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75, 77 and 79-82 as being unpatentable over Van Bree et al., Amalfitano et al., Heus JH and Haseltine et al., are described above. Said references do not specifically teach encoded chimeric polypeptide comprising an erythropoietin secretory signal sequence of SEQ ID NO: 6 linked to human GAA (as in claim 73 in part). Martin et al., specifically teach a therapeutic polypeptide comprising a native human erythropoietin signal peptide of SEQ ID NO: 6 (entire document). It would have been obvious to a person of ordinary skill in the art to combine the teachings of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., and Martin et al., to produce a targeted therapeutic glycoprotein with a an erythropoietin secretory signal sequence (SEQ ID NO: 6) linked to therapeutic polypeptide GAA. Motivation to generate a therapeutic GAA comprising a secretory signal peptide derives from the fact that therapeutic lysosomal enzyme polypeptides are endowed with properties that enable them to be efficiently targeted to sub-cellular compartments such as lysosomes or endoplasmic reticulum and golgi apparatus for post-translational modification of said therapeutic proteins and for efficient processing and transport to the target tissues of interest. The expectation of success is high, because Martin et al., teach the utility of therapeutic polypeptides comprising an erythropoietin secretory signal for effective targeting of said therapeutic polypeptides to clinically significant target tissues. Therefore, claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29,

73, 75, 77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al.,), Amalfitano et al., Heus JH, Haseltine et al., and further in view of Martin et al., (WO 00/47741, 2000).

Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., Martin et al., and further in view of Whitfeld et al., (US Patent No.: 5,298,400, 1994). Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., and Martin et al., are described above. Said references do not specifically teach encoded chimeric polypeptide comprising a α-1-antitrypsin secretory signal sequence of SEQ ID NO: 8 linked to human GAA (as in claim 76 in part). Whitfeld et al., specifically teach a therapeutic polypeptide comprising a α-1-antitrypsin secretory signal sequence of SEQ ID NO: 8 (entire document). It would have been obvious to a person of ordinary skill in the art to combine the teachings of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., Martin et al., and Whitfeld et al., to produce a targeted therapeutic glycoprotein with a an α-1-antitrypsin secretory signal sequence linked to therapeutic polypeptide GAA. Motivation to generate a therapeutic GAA comprising a secretory signal peptide derives from the fact that therapeutic lysosomal enzyme polypeptides are endowed with properties that enable them to be efficiently targeted to sub-cellular compartments such as lysosomes or endoplasmic reticulum and golgi apparatus for post-translational modification of said therapeutic proteins and for efficient processing and transport to the target tissues. The expectation of success is high, because Whitfeld et al., teach the utility of therapeutic polypeptides comprising a α-1-

antitrypsin secretory signal for effective targeting of said therapeutic polypeptides to clinically significant target tissues. Therefore, claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., Martin et al., and further in view of Whitfeld et al., (US Patent No.: 5,298,400, 1994).

Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., Martin et al., Whitfeld et al., and further in view of Meulien P (US Patent No.: 5,521,070, 1996). Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., and Martin et al., are described above. Said references do not specifically teach encoded chimeric polypeptide comprising a Factor IX secretory signal sequence of SEQ ID NO: 9 linked to human GAA (as in claim 76 in part). Meulien P specifically teaches a therapeutic polypeptide comprising a Factor IX secretory signal sequence of SEQ ID NO: 9 (entire document). It would have been obvious to a person of ordinary skill in the art to combine the teachings of Van bree et al., Amalfitano et al., Heus JH, and Meulien P to produce a targeted therapeutic glycoprotein with a Factor IX secretory signal sequence linked to therapeutic polypeptide GAA. Motivation to generate a therapeutic GAA comprising a secretory signal peptide derives from the fact that therapeutic lysosomal enzyme polypeptides are endowed with properties that enable them to be efficiently targeted to sub-cellular compartments such as lysosomes or endoplasmic reticulum and golgi apparatus for post-translational modification of said therapeutic proteins and for efficient processing and transport to the target tissues. The

expectation of success is high, because Meulien P et al., teach the utility of therapeutic polypeptides comprising a Factor IX secretory signal for effective targeting of said therapeutic polypeptides to clinically significant target tissues. Therefore, claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Van Bree et al., Amalfitano et al., Heus JH, Haseltine et al., Martin et al., Whitfeld et al., and further in view of Meulien P (US Patent No.: 5,521,070, 1996).

Therefore, the above references render claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 *prima facie* obvious to one of ordinary skill in the art.

Applicants' have amended the claims and have argued that with the amendments none of the cited references render claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 obvious over prior cited references.

Reply: Examiner has instituted a new rejection and applicants' arguments are relevant to the new rejection. Applicants' arguments have been fully considered but are not deemed persuasive as the cited references indeed render the instant invention obvious over cited prior art, as said references provide the structural elements including an isolated nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to human acid α-glucosidase (GAA), wherein said secretory signal sequence replaces the leader sequence of native human GAA, vectors comprising said polynucleotides and pharmaceutical compositions comprising said vector, motivation and expectation of success.

The cited references are in congruence with the obviousness rejection and teach

all limitations of the instant claims i. e., meet all the criteria and parameters (Teaching, Suggestion and Motivation) as defined by *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according to KSR ruling.

Therefore, the examiner continues to hold the position that the combination of the cited references renders the instant invention obvious for the following reasons. One of ordinary skill in the art would have been motivated to make an isolated nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to human acid α-glucosidase (GAA), wherein said secretory signal sequence replaces the leader sequence of native human GAA as taught by Van Bree et al., using the α-glucosidase (GAA) sequence of SEQ ID NO: 2 of Amalfitano et al., as a therapeutic construct configured in an adeno-associated virus vector and pharmaceutical compositions comprising said vector and further modifying said human acid α-glucosidase (GAA) to comprise any heterologous signal sequence of interest as taught by Heus JH, Haseltine et al., Martin et al., and Meulien P. One of ordinary skill in the art would have been motivated to combine these references because those of ordinary skill would have recognized that a chimeric polypeptide comprising a secretory signal sequence operably linked to human acid α-glucosidase (GAA), wherein said secretory signal sequence replaces the leader sequence of native human GAA could be used for effective targeting of said therapeutic polypeptide to clinically significant target tissues. The expectation of success of merely making an isolated nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to

human acid α-glucosidase (GAA), wherein said secretory signal sequence replaces the leader sequence of native human GAA is high, because methods for constructing vectors configured to express human acid α-glucosidase (GAA) comprising heterologous secretory signal sequences were well known in the art as supported by Van Bree et al., Amalfitano et al., and Heus JH.

The basis for the examniner to continue to hold his position is reasoned below; examiner has provided unequivoical evidence for combining the cited references and that the cited references have been properly applied in this obviousness rejection in accordance with the factual enquires set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according to KSR ruling. Furthermore the cited references teach all the limitations of the instant claims.

The cited references render claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29 and 73, 75-77 and 79-82 *prima facie* obvious to one of ordinary skill in the art when one applies the Teaching, Suggestion and Motivation (TSM) test under the rationale for arriving at a conclusion of obviousness as suggested by the KSR ruling. The rationale applied for this rejection is as follows:

(1) Combining prior art elements according to known method to yield predictable results.

(2) Simple substitution of one known element for another to obtain predictable results.

(3) "Obvious to try"- choosing from a finite number of identified, predictable

solution, with a reasonable expectation of success.

The instant invention is a simple combination of elements taught in the prior art, wherein the elements of prior art are combined to yield predictable results and the choice is from a finite number of identified elements with a highly predictable outcome and expectation of success.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1. Claims 1, 2, 8-11, 18, 21, 22 and 24-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Bree et al., (WO 00/34451, 2000, in IDS) when given the broadest interpretation.

2. Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 *prima facie* obvious and unpatentable over Van Bree et al., (WO 00/34451, 2000, in IDS), in view of Amalfitano et al., (WO 02/098466 A1, 2002, in IDS), Heus JH (US Patent No.: 6,858,425 B1, claiming priority date of Application No.: 09/454,466 filed on 12/03/99), Haseltine et al., (WO 2005/003296 A2, claiming priority date of Application No.: 60/441,305 filed on 01/22/03), Martin et al., (WO 00/47741, 2000), Whitfeld et al., (US Patent No.: 5,298,400, 1994) and Meulien P (US Patent No.: 5,521,070, 1996).

Allowable Subject Matter/Conclusion

None of the allowable. Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 are rejected for the reasons identified in the Rejections and Summary sections of

this Office Action. Applicants must respond to the rejections in each of the sections in this Office Action to be fully responsive for prosecution.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ganapathirama Raghu/
Patent Examiner
Art Unit 1652